REMARKS

Claims 61-88 were pending in the instant application. No claims have been amended, added, or cancelled. For the Examiner's convenience, a copy of the pending claims are submitted herewith as APPENDIX A. No new matter has been added.

Rejection of claims 61-88 Under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph

The rejection of claims 61-88 under 35 U.S.C. §101 has been maintained because, according to the Examiner, "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The rejection of claims 61-88 also stands under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "one skilled in the art clearly would not know how to use the claimed invention." Applicant respectfully traverses these rejections.

The present invention features a novel family of secreted signaling factor proteins, the human CRSP proteins. Four family members have been identified and are described in the instant specification, namely human CRSP-1, CRSP-2, CRSP-3 and CRSP-4 (a murine homologue for CRSP-1 is also described). Claims 61-88 are drawn to the CRSP-2 protein and methods of using same. Applicant has set forth in detail in the prior responses, the various portions of the specification Applicant relies upon to show that the claimed invention meets the requirements of §101 and §112, first paragraph, and those arguments are expressly incorporated herein by reference.

Applicant would like to focus the Examiner on Applicant's teaching in the specification that the CRSP proteins, including the now claimed CRSP-2 protein, are novel secreted soluble signaling proteins involved in modulation of development and differentiation. That the CRSP-2 protein is a secreted soluble signaling factor is evidenced, at least in part, by the fact that the CRSP-2 protein includes hydrophobic signal peptides, is devoid of additional transmembrane domains, and includes abundant and strongly conserved cysteine residues with potential for disulfide cross-linking. CRSP family members are characterized, in particular, by a conserved

cysteine-rich region which includes at least two cysteine-rich domains. Working examples demonstrate that an exemplary family member, CRSP-1, is a secreted protein. By performing structural analysis and sequence comparison, Applicant has further identified signal sequences in CRSP-2, evidencing that CRSP-2 is a secreted protein. Applicant has thus affirmatively shown that CRSP-2 is a secreted soluble signaling protein involved in modulation of development and differentiation. Moreover, this biological function of CRSP-2 was confirmed in Krupnik *et al.*, which is co-authored by the inventor of the present invention. In particular, Applicant directs the Examiner to pages 310-311, Example 3.4, of Krupnik *et al.* which conclusively demonstrates that hDkk-4, which is the same protein as CRSP-2 (*i.e.*, not an ortholog), modulates head induction based on experiments in which the authors injected hDkk-4 mRNA into developing *Xenopus* embryos and determined that the injected hDkk4 was capable of inhibiting Wnt-induced axis duplication. Thus the protein that was used in Krupnik *et al.* in Example 3.4, is the exact same protein that Applicant is now claiming, and was in possession of at the time of filing.

To further support this position, Applicant submits herewith yet another reference, Mao, B. *et al.*, *Gene* 302:179-183 (2003), which further confirms that CRSP-2 (referred to as Dkk4), inhibits Wnt signaling, thereby inhibiting Wnt-induced axis duplication (see, *e.g.*, Example 3.1 on page 180).

The Examiner states in the March 13, 2000 office action that "the instant specification is silent with respect to Wnt signaling and the role of CRSP proteins and that the specification does not mention Dkk proteins." Applicant directs the Examiner to page 1, lines 25-28 of the specification, which describes that Wnt proteins are "recognized as one of the major families of developmentally important signaling molecules..." and cites a journal reference, which is incorporated by reference (see, p. 69, lines 16-19 of the specification). The application is therefore not "silent with respect to Wnt signaling." Moreover, Applicant states on page 11, lines 10-12, that CRSP activity may be indirect, "such as a cellular signaling activity mediated by interaction of the CRSP protein with a second protein (e.g. a CRSP receptor)." In addition, at page 11, lines 18-20, Applicant states that CRSP activity may be a "complex formation between

a second soluble CRSP binding partner, wherein the CRSP binding partner is a non-CRSP protein molecule." Applicant has thus described the CRSP-2 activity and this activity has been confirmed by post-filing evidence.

Moreover, Applicant submits that whether the specification describes the Wnt signaling pathway or Dkk proteins, per se, is irrelevant to the analysis of whether Applicant has sufficiently described a credible utility and taught how to make and use the invention. The fact that CRSP-2 inhibits Wnt signaling is merely the mechanism by which CRSP-2 acts. As the Examiner is well aware, one need not completely understand the mechanism underlying the claimed invention. Likewise, whether "Dkk proteins" per se, are mentioned in the specification is also irrelevant to the present §101/§112 analysis; whether or not consistent nomenclature is used does not change the fact that Dkk-4 is the same protein as CRSP-2, which Applicant was in possession of at the time of filing, and has been conclusively found to be a secreted soluble signaling protein involved in modulation of development and differentiation, as stated by Applicant in the specification.

Finally, the Examiner appears to be relying on the phraseology used by the Krupnik *et al.* authors wherein the words "may" and "might" are used, to support his position. Applicant submits that such phraseology is standard in peer review scientific references and does not refute the experimental evidence which conclusively supports Applicant's stated biological function for CRSP-2. Applicant is not relying on the publication to establish an activity and/or utility for the claimed invention, but to further evidence the credibility of Applicant's prior assertions of utility.

In summary, Applicant has stated a credible utility for the CRSP-2 protein and post-filing evidence confirms the stated utility. The §101/§112 rejections are therefore improper and should be withdrawn.

With respect to the issue raised by the Examiner regarding the IDS, Applicant will re-file the IDS, PTO-1449 and references.

With respect to the Examiner's comments regarding the blanks in the specification, Applicant refers the Examiner to the Amendment and Response filed August 14, 2000, which amended the specification to remove the blanks.

CONCLUSION

In view of the foregoing amendments and following remarks, it is respectfully submitted that the application is in condition for allowance. If the Examiner has any questions or believes that a telephone conversation with Applicant's Attorney would be helpful in expediting allowance of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

DeAnn F. Smith, Esq.
Reg. No. 36,683
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Fax (617) 742-4214

Dated: **March 17, 2003**

APPENDIX A

61. A method for identifying a compound that modulates the activity of a CRSP protein, comprising:

a. providing a indicator composition comprising a protein having CRSP-2 activity;

b. contacting the indicator composition with a test compound; and

c. determining the effect of the test compound on CRSP-2 activity in the indicator composition to thereby identify a compound that modulates the activity of an CRSP-2 protein.

62. An isolated polypeptide comprising an amino acid sequence at least 80% identical to an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO:5 and the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

63. The polypeptide of claim 62, which comprises an amino acid sequence which is at least 90% identical to an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO:5 and the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

64. The polypeptide of claim 62, wherein the amino acid sequence comprises a cysteine-rich region.

65. The polypeptide of claim 62, wherein the amino acid sequence comprises a cysteine-rich domain.

66. An isolated polypeptide comprising a cysteine-rich region which is at least 80% identical to amino acids 41 to 218 of SEQ ID NO:5.

67. The polypeptide of claim 66, wherein the cysteine-rich region comprises amino acids 41 to 218 of SEQ ID NO:5.

68. An isolated polypeptide comprising a cysteine rich domain which is at least 80% identical to amino acids 41 to 90 of SEQ ID NO:5 or to amino acids 138 to 218 of SEQ ID NO:5.

69. The polypeptide of claim 68, wherein the cysteine-rich domain comprises amino acids 41 to 90 of SEQ ID NO:5 or amino acids 138 to 218 of SEQ ID NO:5.

70. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5.

71. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

72. An isolated polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:4.

73. An isolated polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:6.

74. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of incubation at 45°C in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 50°C.

75. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of incubation at 45°C in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 65°C.

76. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 80% identical to the nucleotide sequence consisting of SEQ ID NO:6.

77. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence consisting of SEQ ID NO:6.

78. An isolated polypeptide comprising at least 10 consecutive amino acids of the amino acid sequence of SEQ ID NO:5.

79. The polypeptide of claim 78, which comprises at least 25 consecutive amino acids of SEQ ID NO:5.

80. The polypeptide of claim 79, which comprises at least 50 consecutive amino acids of SEQ ID NO:5.

81. The polypeptide of claim 80, which comprises at least 100 consecutive amino acids of SEQ ID NO:5.

82. The polypeptide of claim 81, which comprises a cysteine-rich domain of SEQ ID NO:5.

83. The polypeptide of claim 80, which comprises a cysteine-rich region of SEQ ID NO:5.

84. The polypeptide of claim 82, wherein the cysteine-rich domain comprises amino acids 41 to 90 of SEQ ID NO:5 or amino acids 138 to 218 of SEQ ID NO:5.

85. The polypeptide of claim 81, wherein the cysteine-rich region comprises amino acids 41 to 218 of SEQ ID NO:5.

86. An isolated polypeptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO:5 and SEQ ID NO:5 without amino acids 1 to 19.

87. A fusion polypeptide comprising the polypeptide of any one of claims 62, 66, 68, 72-76 and 78, operatively linked to a non-CRSP polypeptide.

88. A pharmaceutical composition comprising the polypeptide of any one of claims 62, 66, 68, 72-76 and 78 and a pharmaceutically acceptable carrier.